PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
G01N 27/26, A61B 5/00, 5/05, 19/00, C12Q 1/00, 1/54, 21/06, C12N 9/00, 1/00, 1/20, C12M 1/40, 1/34, A61F 13/20, A61N 1/30, A61K 9/22

A1

(11) International Publication Number: **WO 97/19344**

(43) International Publication Date: 29 May 1997 (29.05.97)

(21) International Application Number: PCT/US96/18724

(22) International Filing Date: 21 November 1996 (21.11.96)

(30) Priority Data:
08/561,972 22 November 1995 (22.11.95) US

(71) Applicant *(for all designated States except US)*: LEGACY GOOD SAMARITAN HOSPITAL AND MEDICAL CENTER [US/US]; 1919 N.W. Lovejoy Street, Portland, OR 97209 (US).

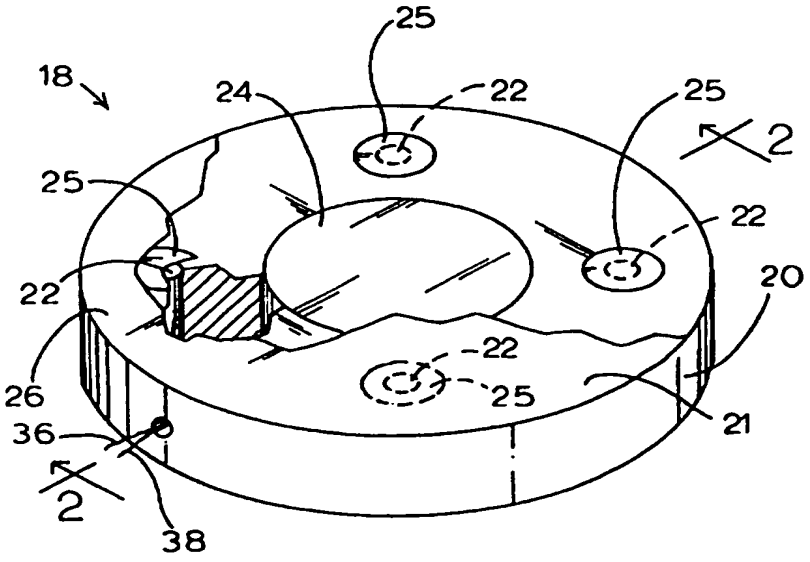
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: WARD, W., Kenneth [US/US]; 365 S.W. Breeze Court, Portland, OR 97225 (US). WILGUS, Eric, S. [US/US]; 2207 N.E. 12th Avenue, Portland, OR 97212 (US).

(74) Agents: VAN RYSSELBERGHE, Pierre, C. et al.; Kolisch, Hartwell, Dickinson, McCormack & Heuser, 520 S.W. Yamhill Street, Portland, OR 97204 (US).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: DEVICE FOR MONITORING CHANGES IN ANALYTE CONCENTRATION



(57) Abstract

The invention provides an electrochemical sensor system for measuring analyte concentrations in a fluid sample. The invention is particularly useful for measuring analytes such as glucose in a patient. An implantable glucose sensor (18) includes a disc shaped body (20) containing multiple anodes (22) on opposing sides of the body (20). Electrodes (22, 24) are connected to a transmitter (130) which transmits radio signals to an external receiver (134) and computer (138) where data is processed to yield glucose concentration figures.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

DEVICE FOR MONITORING CHANGES IN ANALYTE CONCENTRATION

Field of the Invention

The invention relates to electrochemical systems for measuring analyte concentration. In particular, the invention involves a sensor including electrodes under a semi-permeable membrane for monitoring analyte concentrations in fluids surrounding the sensor.

Background

There are many instances when it is necessary to monitor the concentration of molecules ("analytes") in a fluid. For example, glucose levels must be frequently monitored in persons with diabetes so that appropriate doses of insulin can be administered in a timely manner. Many other analytes are measured commonly in human blood and in other fluids.

A variety of methods and devices for measuring analytes in fluids have been devised. One such device, referred to as an electrochemical sensor, typically includes oppositely charged electrodes under a semi-permeable membrane. Depending on what analyte is being monitored, membranes, enzymes and/or other appropriate materials are provided around the electrodes so that analyte reaction and transport from the fluid surrounding the sensor is controlled. Oxidative and reductive reactions take place at or near the electrodes, thus causing electron potentials measured as changes in current which may be correlated to the concentration of analyte in the fluid.

Electrochemical sensors have been used to measure glucose in human blood for a long time. Most of these sensors are designed to measure glucose in a blood sample which has been drawn or extracted from the patient. For patients such as people with diabetes who must test blood glucose levels as often as several times per day, the regular blood drawing process (typically by finger tip puncture) becomes quite cumbersome, messy and even painful. The diabetic must carry special equipment for extracting blood. Some patients fail to test as frequently as they should because of problems associated with the blood extracting process.

Therefore, it has been recognized for a long time that an implanted glucose sensor would offer the important advantage of avoiding the need for repeated blood extraction. However, there are other problems which must be addressed with an implantable sensor. First, there must be a mechanism for accessing raw electrical data generated by the sensor under the patient's skin. Protruding wires are undesirable because they are cumbersome, prone to causing infection and sometimes painful. Accordingly, it is preferable to include a wireless data transmission (telemetry) device coupled to the sensor in a single implantable unit so that no trans-dermal wires are required.

Second, an implanted sensing unit may cause internal trauma, i.e., bruising or bleeding from the patient's routine movement or contact with his or her environment, especially if the sensing unit is large or thick or if it is geometrically shaped with any sharp points or edges.

Another problem associated with implantable sensors is that over time (days and weeks) a cellular coat tends to develop around the sensor which may eventually block the analyte of interest from contacting the electrodes, thus causing the sensor to fail.

For these reasons, and perhaps other reasons, researchers in the field have been unsuccessful in their attempts to produce an implantable sensor unit which is capable of functioning satisfactorily for a sufficient period of time to justify the expense and inconvenience of producing and surgically implanting the sensing hardware.

A viable implantable glucose sensor should provide reliable performance for at least 1-2 months, preferably three months or more. During its useful life, the device should generate a predictable dose response over a concentration range of approximately 40 to 400 milligrams per deciliter (mg/dl). The device should exhibit a lag time between a concentration change and the resulting signal output of less than 20 minutes, preferably less than 10 minutes. The sensor should be relatively insensitive to potential interfering substances such as ascorbic acid and acetaminophen. The device should be relatively accurate for at least several days after calibration (stability). Glucose measurement with the sensor should be precise to at least within approximately 10 mg/dl. The sensor should be incorporated in an implantable unit which is capable of wireless data transmission, and which is dimensioned so as to minimize surgical complication and risk of pain, bruising or other internal trauma.

Summary of the Invention

The objectives stated above are achievable with the device and system of the present invention which includes a device for electrochemically sensing changes in the concentration of an analyte of interest.

In one embodiment of the invention, the device includes a sensor body having two opposing sides. Each side of the body includes at least one, preferably several, anode(s) and at least one cathode spaced apart from each other and covered by a membrane which is semi-permeable to the analyte of interest. In a preferred sensor design for measuring glucose, plural anodes are disposed on two opposing sides of a disc-shaped sensor body. The anodes are covered by an enzyme layer including glucose oxidase and an outer semi-porous membrane layer made of a material such as Parylene™ ("PPX") or Chronoflex™ AR ("CAR").

In another embodiment of the invention, the sensor body contains a plurality of electrode pairs, each pair including an anode and a cathode. The electrode may take the form of points or lines. In one design linear electrodes are arranged in a "spoke-like" configuration. The electrode pairs preferably are disposed on both sides of the body.

An implantable glucose sensor, according to the present invention, may be electrically coupled to a transmitter which includes a power source, for example a battery. The transmitter is capable of converting data signals from the sensor into corresponding radio signals. A receiver is provided remotely from the sensor for receiving the radio signals. A processor is

connected to the receiver and used to interpret the radio signals, to yield analyte concentration figures.

The present invention also provides a method of making an analyte sensor. A substantially disc-shaped body is provided with two opposing sides. At least one cathode and plural anodes are created on each side of the body. A semi-permeable membrane is deposited on the electrodes. When the method is employed to make a glucose sensor, the enzyme layer including glucose oxidase is created between the anodes and the semi-permeable membrane. An interferent retarding layer may be created between the anodes and the enzyme layer.

Description of the Figures

Figure 1 is a partially cut-away perspective view of an analyte sensor in accordance with a preferred embodiment of the present invention.

Figure 2 is a cross-sectional view of the sensor shown in Figure 1.

Figure 3 is a top view of an analyte sensor in accordance with a second embodiment of the present invention.

Figure 4A is a top view of an analyte sensor employing linear electrodes in accordance with a third embodiment of the present invention.

Figure 4B is a partial cross-sectional view of the sensor shown in Figure 4A.

Figure 5 is a top view of another analyte sensor in accordance with a fourth embodiment of the present invention.

WE CLAIM:

1. A device for electrochemically sensing changes in the concentration of an analyte of interest comprising

a body having a pair of spaced facial expanses, each expanse of the body including at least one anode and at least one cathode spaced apart from each other and covered by a membrane which is semi-permeable to the analyte of interest.

2. The device of claim 1 wherein the analyte of interest is glucose.

3. The device of claim 2 wherein each expanse is at least partially covered by an enzyme layer including glucose oxidase between the anode and the membrane.

4. The device of claim 1 wherein the membrane comprises polyparaxylxylene.

5. The device of claim 1 wherein each expanse of the body includes a plurality of anodes.

6. The device of claim 5 wherein each expanse of the body has a plurality electrode pairs, each electrode pair including one anode and one cathode.

7. The device of claim 6 wherein each expanse of the body has four electrode pairs.

8. The device of claim 7 wherein the body is disk-shaped.

9. The device of claim 3 wherein each expanse of the body has an interferent retarding layer between the anode and the enzyme layer.

10. A device for electrochemically sensing changes in the concentration of an analyte of interest comprising

a body including at least one anode and at least one cathode, and

a membrane comprising polyparaxylxylene or a carbonate-based polyurethane covering the anode.

11. The device of claim 10 further comprising a layer including glucose oxidase disposed between the anode and the membrane, the device being capable of sensing changes in glucose concentration of a fluid surrounding the device.

12. The device of claim 10 wherein the body has two opposing sides, each side of the body having at least one anode and at least one cathode.

13. The device of claim 12 wherein each side of the body has a plurality of anodes.

14. The device of claim 13 wherein each side of the body has a plurality of cathodes, each cathode being paired with one of the anodes.

15. A device for electrochemically sensing the concentration of an analyte of interest comprising

a body having a plurality of electrode pairs, each pair including an anode and a cathode.

16. The device of claim 15 wherein the body has two opposing sides, the electrode pairs being distributed on both sides of the body.

17. The device of claim 16 wherein the body is disk-shaped.

18. The device of claim 16 wherein each side of the body has at least four electrode pairs.

19. The device of claim 15 wherein the anodes lead to a common anode conductor and the cathodes lead to a common cathode conductor.

20. The device of claim 15 wherein the analyte of interest is glucose and each anode is covered with an enzyme layer comprising glucose oxidase.

21. An implantable device for electrochemically sensing changes in the concentration of an analyte of interest, and transmitting signals indicative of the concentration changes, comprising

a transmitter including a power source,

a sensor electrically coupled to the transmitter, the sensor including a disk-shaped body having two opposing sides, each side of the body having and a cathode and a plurality of anodes, whereby the combined transmitter and sensor can be implanted in a mammal for wireless transmission of data indicative of analyte concentration to an external receiver.

22. The device of claim 21 wherein the analyte of interest is glucose.

23. The device of claim 22 further comprising

an enzyme layer comprising glucose oxidase covering the anodes, and

a membrane semi-permeable to glucose covering the enzyme layer.

24. The device of claim 21 further comprising an amplifier and an electrometer, the cathodes and anodes from the sensor being connected to the amplifier and the electrometer converting current signals into voltage signals before transmitting corresponding data signals to an external processing device.

25. The device of claim 21 further comprising an analog-to-digital converter connected to the sensor for converting analog signals indicative of current changes into digital signals prior to transmitting corresponding data to an external receiver.

26. An analyte concentration monitoring system comprising

a sensor including a body having two opposing sides, each side of the body having at least one cathode, plural anodes and a semi-permeable membrane covering the anodes, the sensor being capable of generating analog data signals indicative of analyte concentration in a fluid surrounding the sensor,

a transmitter including a power source, the transmitter being electrically coupled to the sensor and capable of converting the data signals into corresponding radio transmission signals

a receiver for receiving the radio transmission signals at a remote location.

27. The system of claim 26 further comprising a processor connected to the receiver for interpreting and converting the radio transmission signals into analyte concentration information.

28. A method of making an implantable analyte sensor comprising

providing a body having two opposing sides,

creating at least one cathode and plural anodes on both sides of the body, and

depositing a semi-permeable membrane on the cathodes and anodes.

29. The method of claim 28 wherein the analyte is glucose, further comprising depositing an enzyme layer including glucose oxidase on the anodes before the step of depositing the semi-permeable membrane.

30. The method of claim 28 comprising depositing a layer of polyparaxylxylene or ChronoflexÔ AR on the enzyme layer.

31. The method of claim 28 comprising forming the body in the shape of a disk.

32. The method of claim 29 further comprising electrically coupling the sensor to a radio transmitter.

33. The method of claim 32 further comprising

implanting the sensor and transmitter into a mammal,

sensing glucose concentration changes,

transmitting corresponding radio signals to a remote receiver, and

processing and interpreting the radio signals into glucose concentration data.

34. A system for monitoring analyte concentrations in the blood of a mammal comprising

an organization of implantable sensors, each sensor including an anode and a cathode covered by a membrane which is semi-permeable to the analyte.

35. The system of claim 34 wherein the analyte is glucose, further comprising an enzyme layer between the anodes and the membrane.

36. The system of claim 34 further comprising a body substantially containing all of the sensors.

37. The system of claim 36 wherein the body is substantially disk shaped and has two opposing sides, the sensors being disposed on both sides of the body.

38. The system of claim 37 wherein each side of the body has four sensors.

39. The system of claim 34 further comprising a plurality of bodies, each sensor being provided in a separate body.

40. The system of claim 34 wherein all anodes lead to a common anode conductor and all cathodes lead to a common cathode conductor.

41. A device for sensing changes in the concentration of an analyte of interest comprising

a body,

an analyte detection mechanism contained within the body, and

a fibrotic coat interference inhibitor in close proximity to the body for decreasing interference with analyte detection due to formation of a fibrotic coat around the body.

42. The device of claim 41 wherein the analyte is glucose.

43. The device of claim 41 wherein the inhibitor has the property of decreasing the rate of collagen deposition on the body.

44. The device of claim 41 wherein the inhibitor has the property of increasing vascularity in a fibrotic coat.

45. The device of claim 41 wherein the inhibitor is a steroid.

46. The device of claim 41 wherein the inhibitor is a vascular growth factor.

47. The device of claim 45 wherein the inhibitor is selected from the group consisting of dexamethasone, relaxin and gamma interferon, or mixtures thereof.

48. The device of claim 46 wherein the inhibitor is selected from the group consisting of vascular endothelial growth factor, endothelial cell growth factor, and mixtures thereof.

49. The device of claim 41 wherein the inhibitor is incorporated in a polymer matrix which provides controlled relatively constant release of the inhibitor over time into tissue surrounding the body.

50. The device of claim 49 wherein the polymer matrix includes a material selected from the group consisting of polydimethylsiloxane, poly-l-lactic acid, polyglycolic lactic acid and mixtures thereof.

51. The device of claim 50 wherein the polymer matrix is in the form of a tape impregnated with the inhibitor.

52. The device of claim 41 wherein the body is substantially disk shaped.

53. The device of claim 52 wherein the body has a peripheral edge, the inhibitor being impregnated in a time-release polymer matrix associated with the peripheral edge of the body.

54. The device of claim 41 wherein the inhibitor is dexamethasone.

55. The device of claim 49 wherein the inhibitor comprises dexamethasone and the polymer matrix comprises polydimethylsiloxane.

56. The device of claim 41 wherein the body has a pair of spaced facial expanses, each expanse of the body including at least one anode and at least one cathode spaced apart from each other and covered by a membrane which is semi-permeable to the analyte of interest.

57. The device of claim 56 wherein the analyte of interest is glucose.

58. The device of claims 1,2,3,4,5,6,7,8 or 9 further comprising a fibrotic coat interference inhibitor in close proximity to the body for decreasing interference with analyte detection due to formation of a fibrotic coat around the body.

59. The device of claim 58 wherein the inhibitor is a corticosteroid or a growth factor.

60. The device of claim 41 wherein the effective dose of inhibitor is large enough to significantly decrease interference with analyte detection caused by fibrotic capsule formation, but small enough to avoid adverse systemic effects.

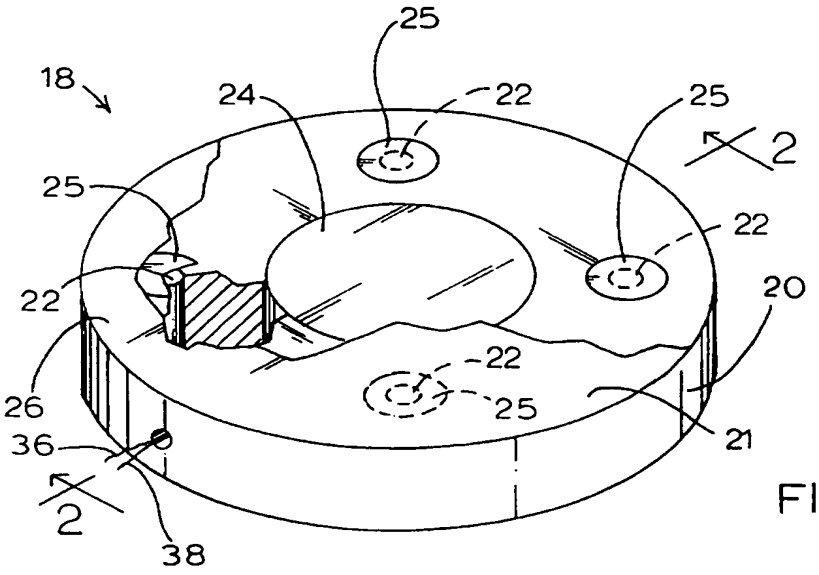


FIG.1

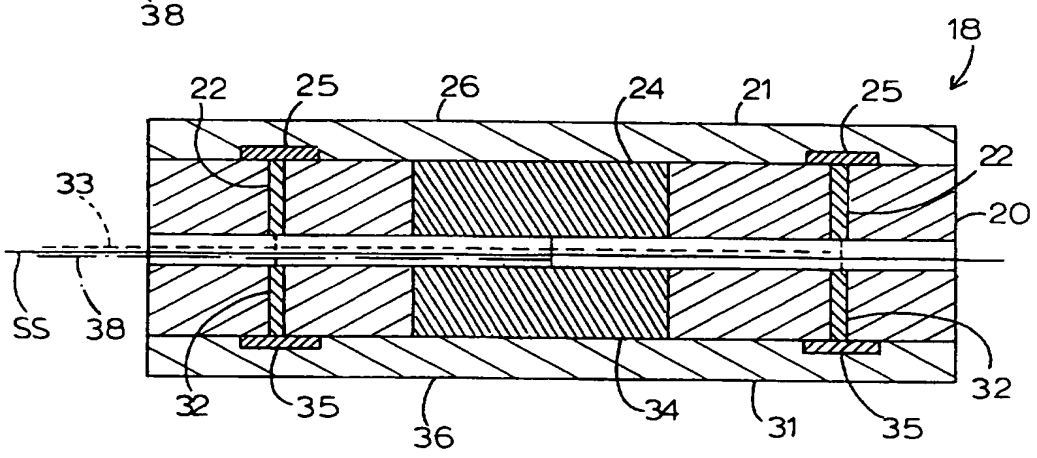


FIG. 2

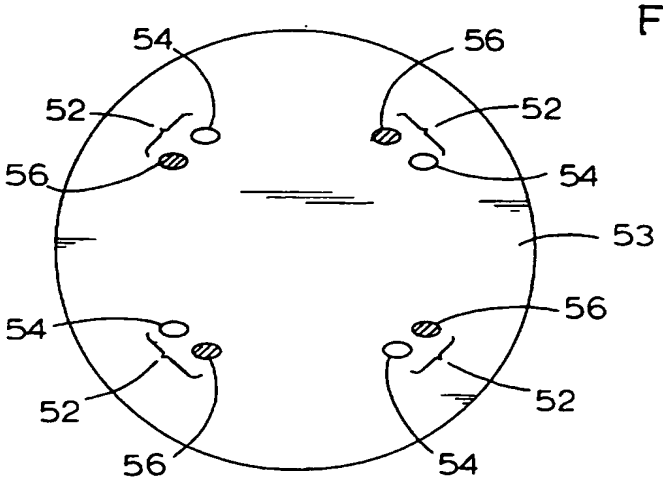


FIG. 3

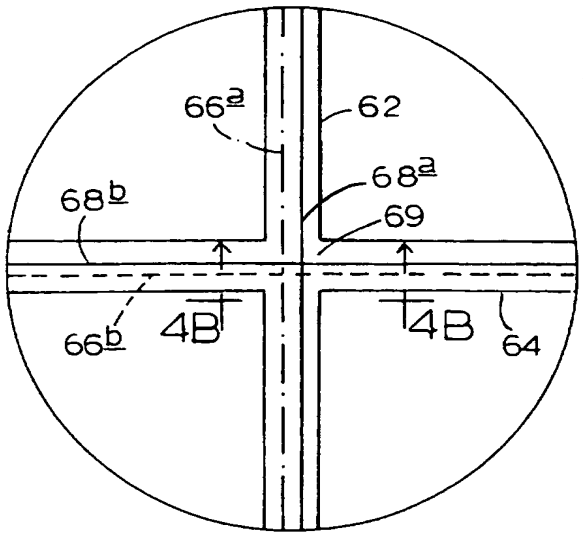


FIG. 4A

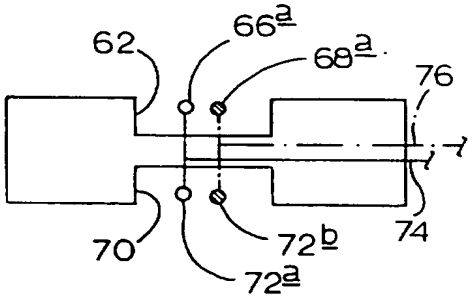


FIG. 4B

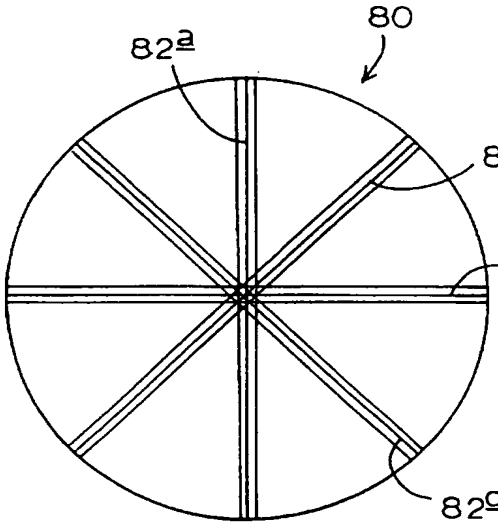


FIG. 5

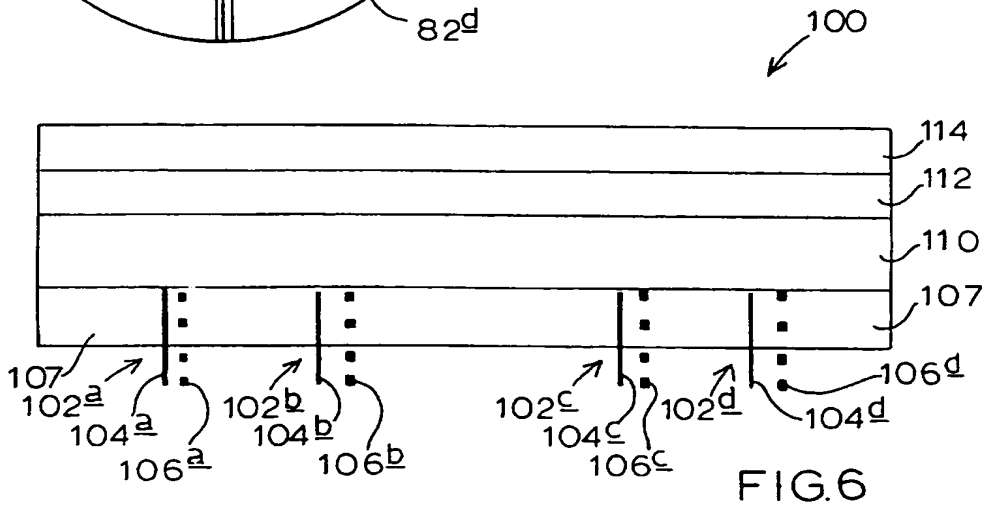


FIG. 6

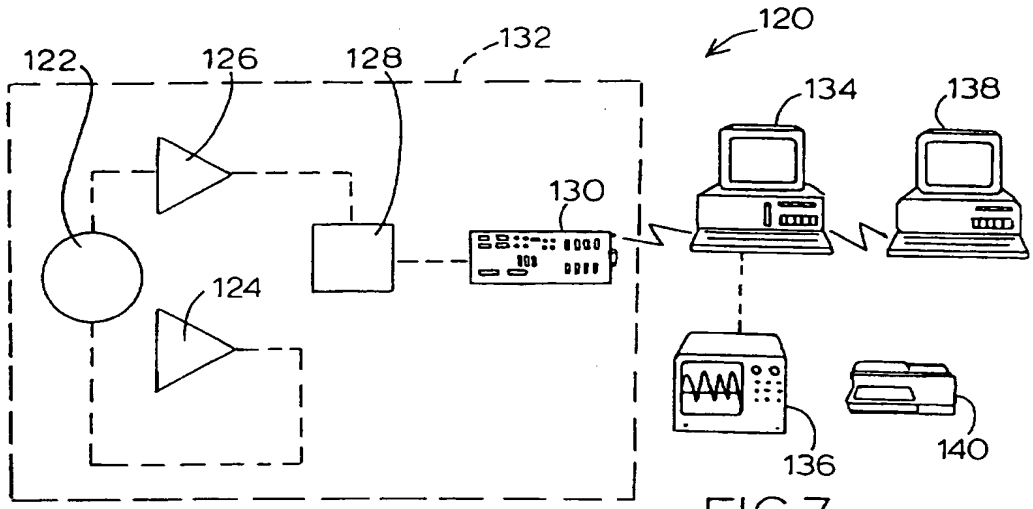


FIG.7

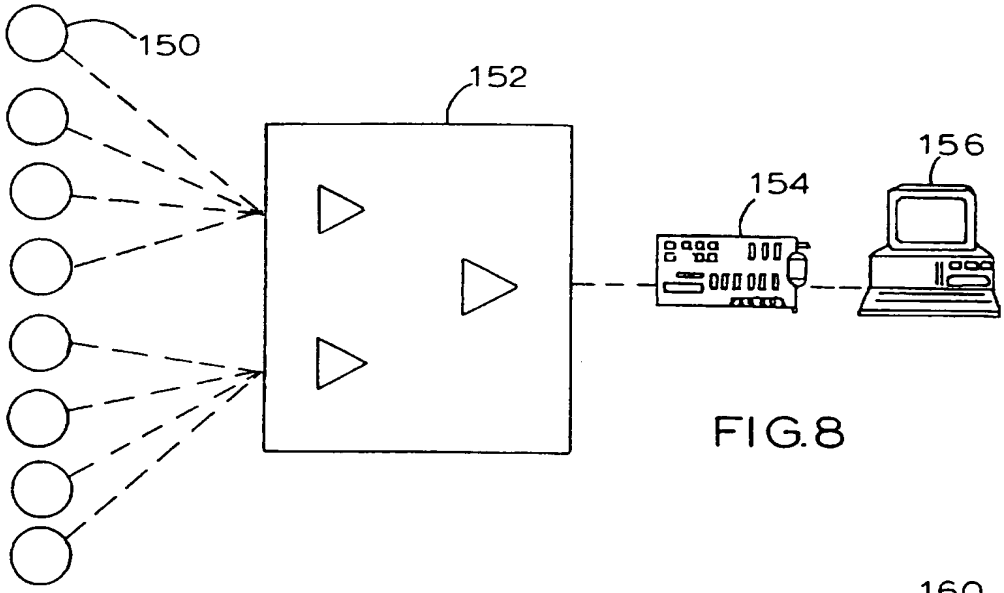


FIG.8

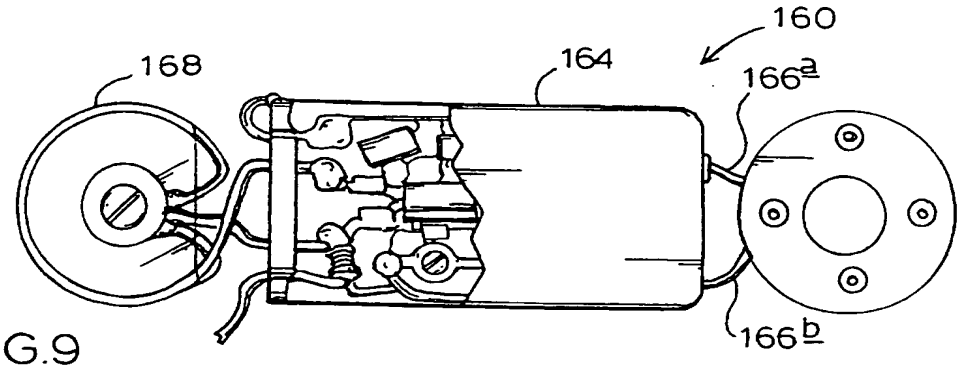


FIG.9

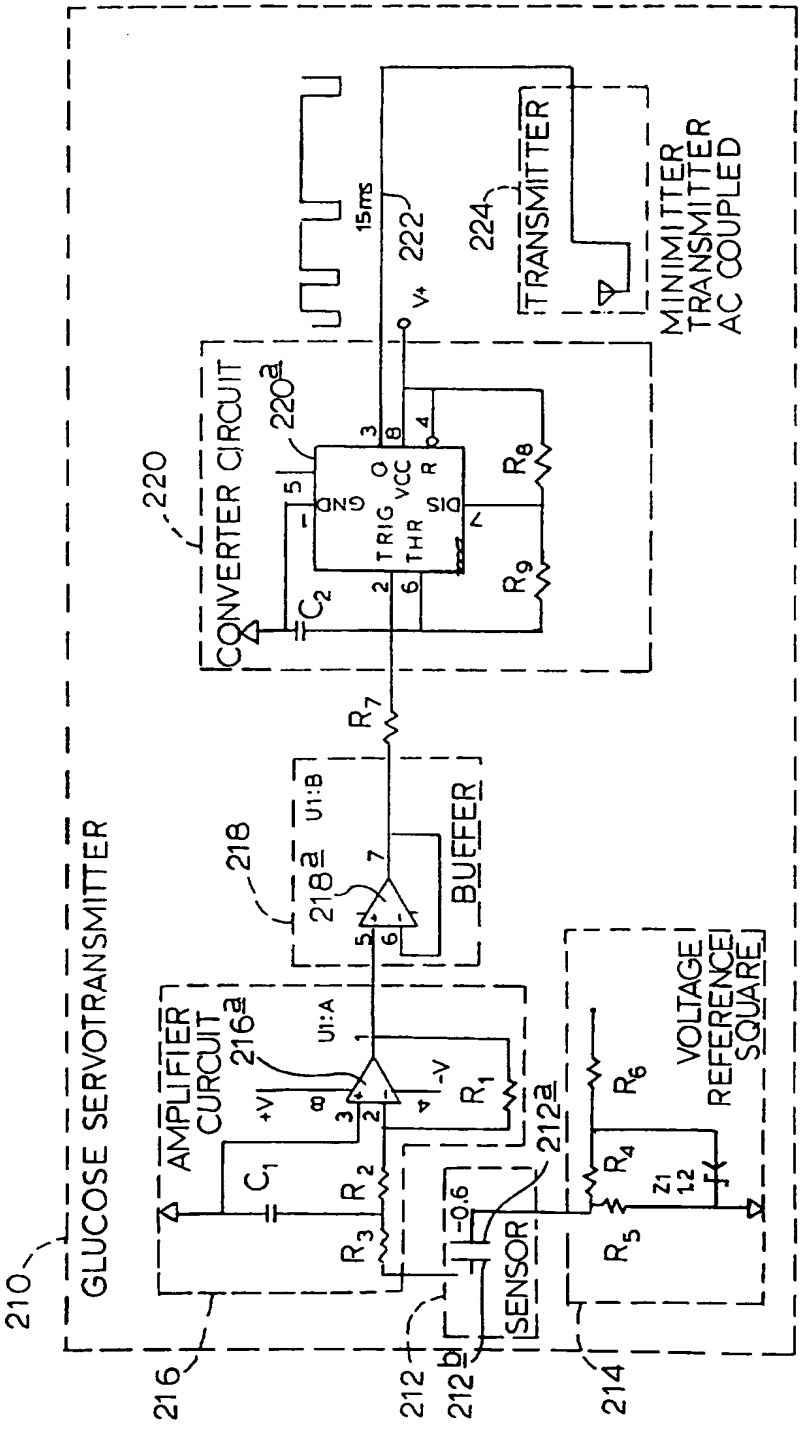

GLUCOSE SERVOTRANSMITTER
210
AMPLIFIER CURCUIT
216a
U1:A
+V
-V
C1
R1
R2
R3
216
BUFFER
218
218a
U1:B
R7
CONVERTER CIRCUIT
220
220a
15ms
222
V+
TRIG
THR
VCC
R
Q
GND
R8
R9
C2
TRANSMITTER
224
MINIMITTER TRANSMITTER AC COUPLED
VOLTAGE REFERENCE SQUARE
R4
R5
R6
Z1
1.2
212a
212b
-0.6
SENSOR
212
214

FIG.10

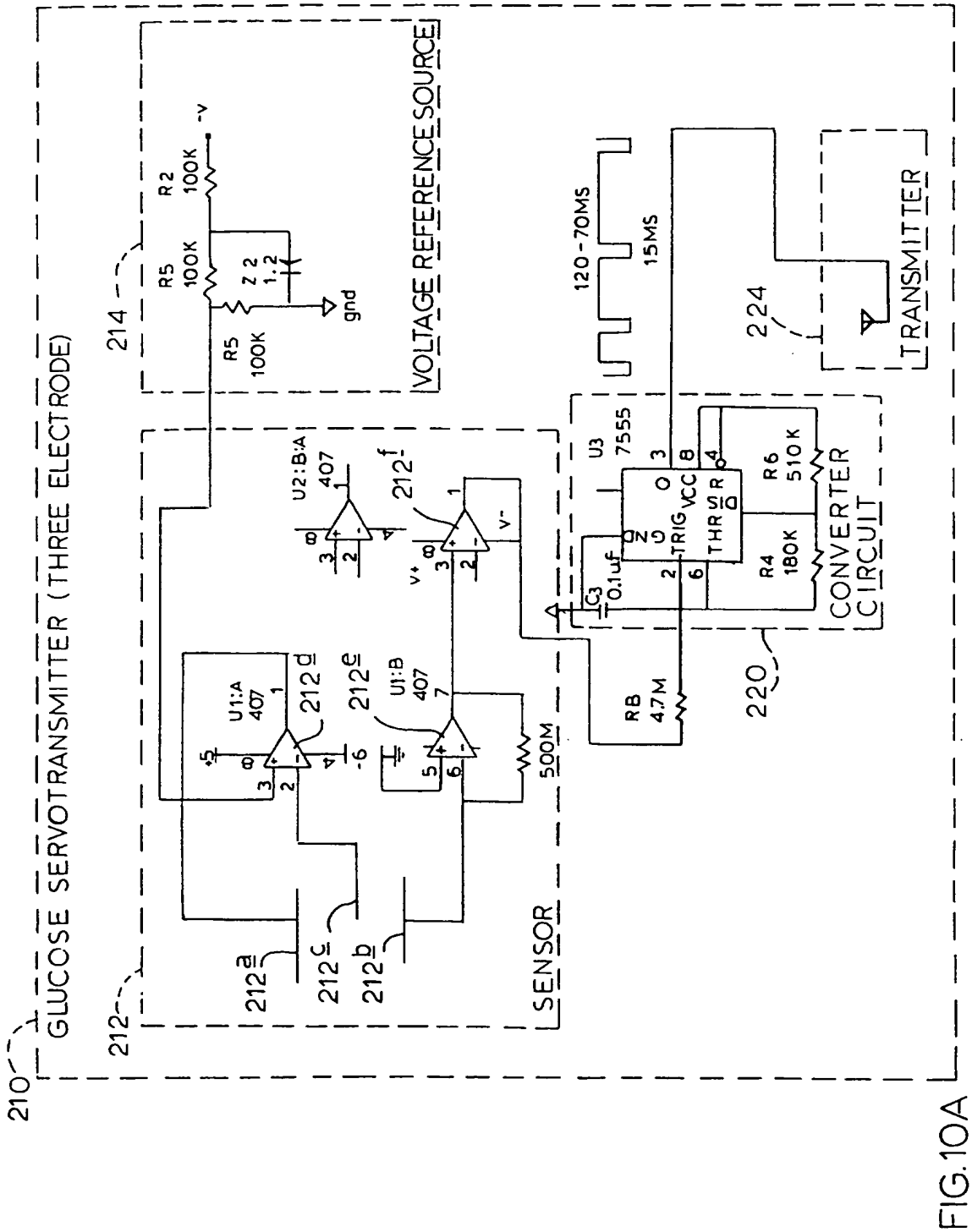

GLUCOSE SERVOTRANSMITTER (THREE ELECTRODE)
210
212
SENSOR
212a
212b
212c
212d
212e
212f
U1:A 407
U1:B 407
U2:B:A 407
500M
VOLTAGE REFERENCE SOURCE
214
R2 100K
R5 100K
R5 100K
Z 2 1.2
gnd
-V
V+
V-
U3 7555
GND
TRIG
OUT
RST
VCC
DIS
THRS
C3 0.1uf
RB 4.7M
R4 180K
R6 510K
CONVERTER CIRCUIT
220
120-70MS
15MS
224
TRANSMITTER

FIG.10A

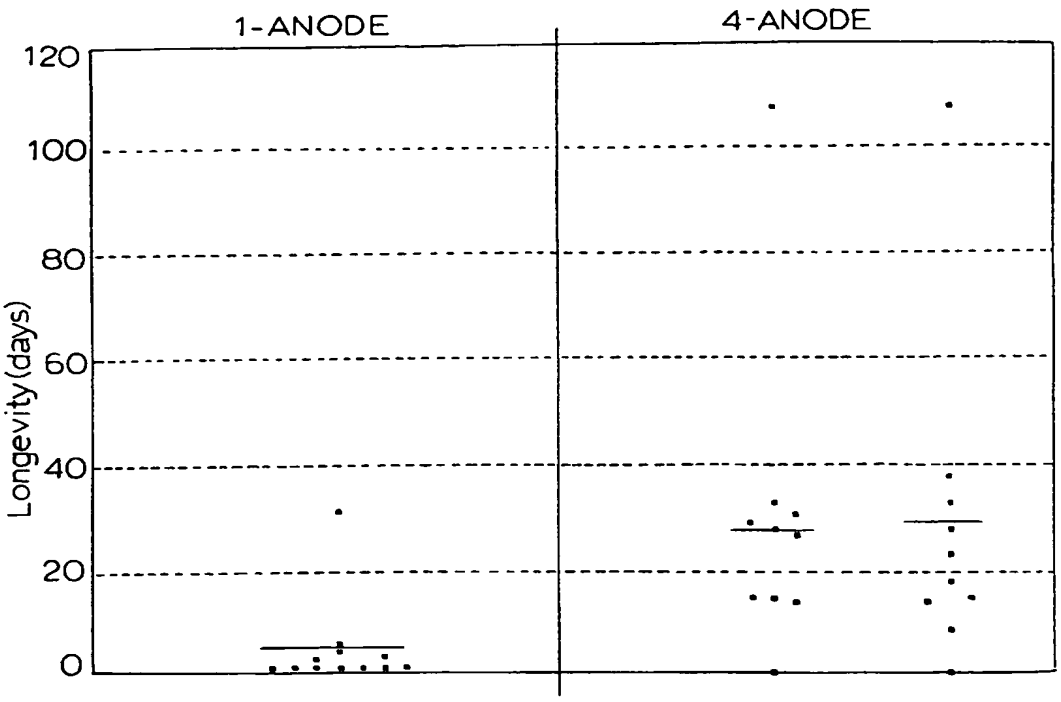

1-ANODE
4-ANODE
120
100
80
60
40
20
0
Longevity (days)

FIG.11

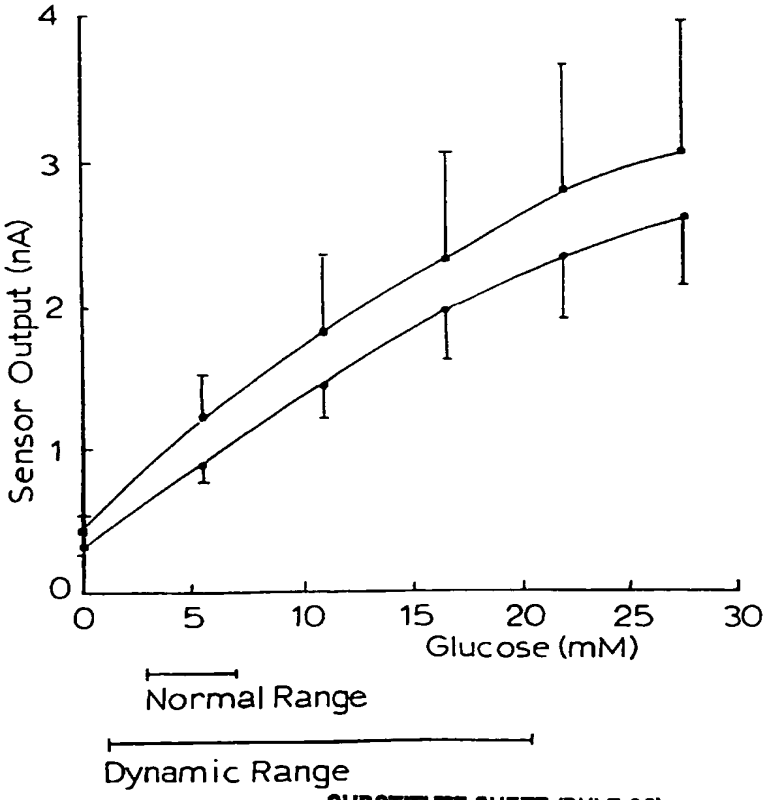

4
3
2
1
0
Sensor Output (nA)
0
5
10
15
20
25
30
Glucose (mM)
Normal Range
Dynamic Range

FIG.12

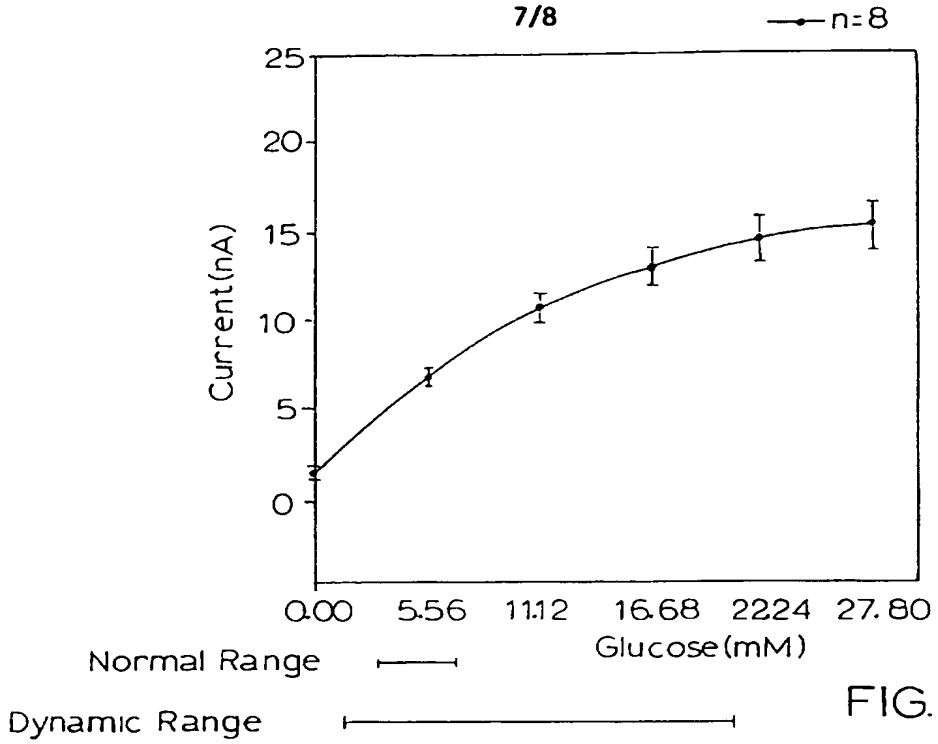

n=8
25
20
15
10
5
0
Current(nA)
0.00
5.56
11.12
16.68
22.24
27.80
Glucose(mM)
Normal Range
Dynamic Range

FIG. 13

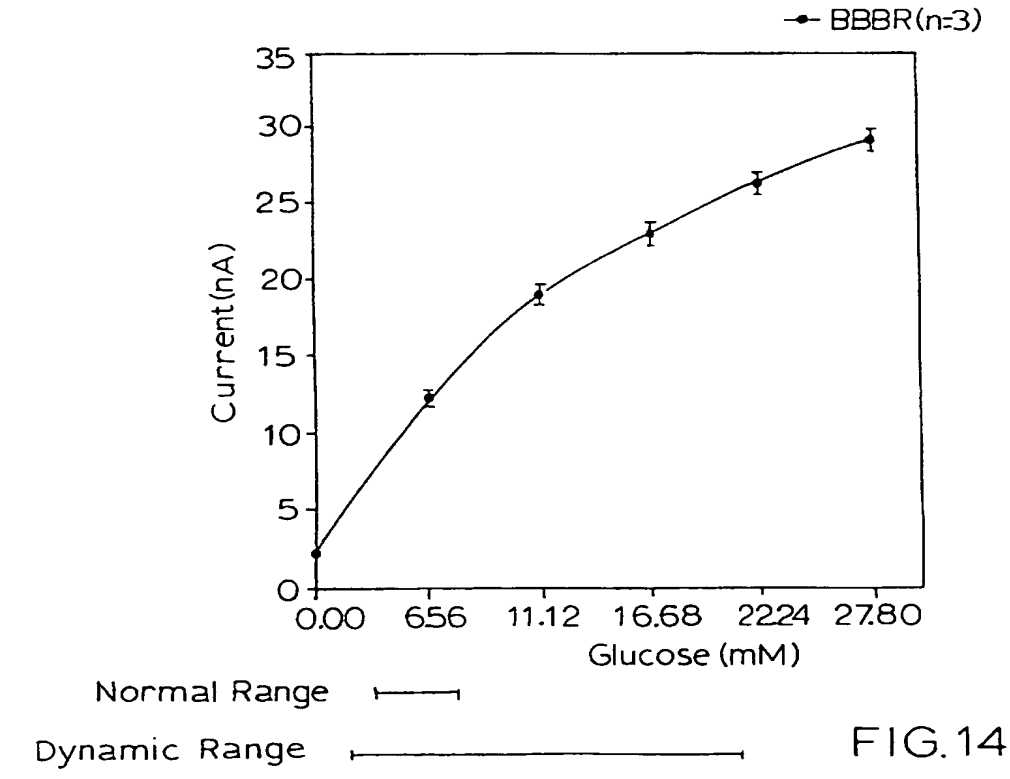

BBBR(n=3)
35
30
25
20
15
10
5
0
Current(nA)
0.00
6.56
11.12
16.68
22.24
27.80
Glucose (mM)
Normal Range
Dynamic Range

FIG. 14

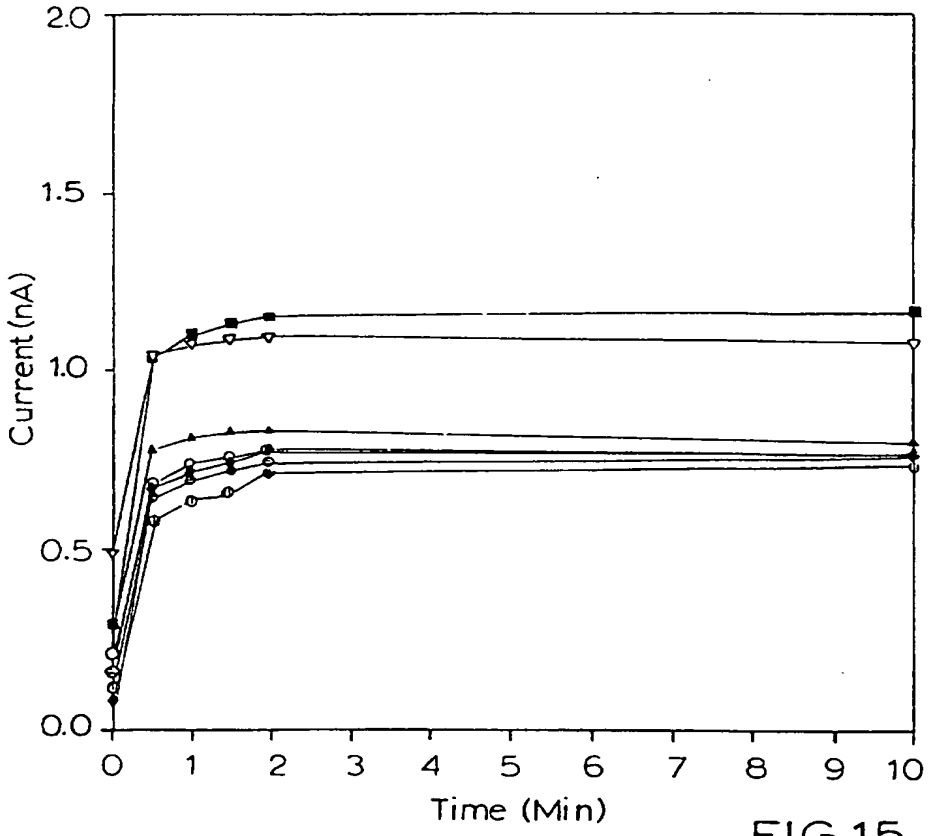


FIG 15

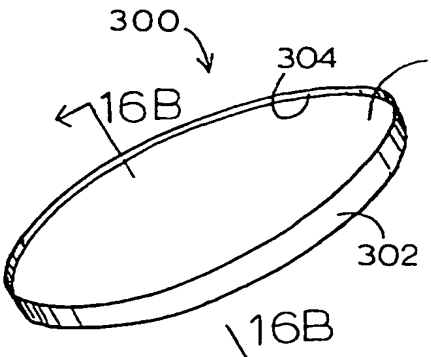


FIG.16A

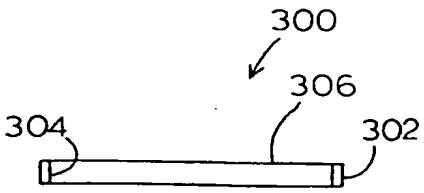


FIG.16 B